



CHEMICAL MANUFACTURERS ASSOCIATION

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March 23, 1998

Dr. C.W. Jameson
National Toxicology Program
Report on Carcinogens
MD EC-14
P.O. Box 12233
Research Triangle Park, NC 27709

Re: Comments on National Toxicology Program Proposed Classification
of Ethylene Oxide as a Known Carcinogen
63 Fed. Reg. 5565 (February 3, 1998)

Dear Dr. Jameson:

This letter and the enclosed comments are submitted on behalf of the Chemical Manufacturers Association Ethylene Oxide Industry Council (EOIC). EOIC appreciates this opportunity to submit comments on the National Toxicology Program's proposed classification of ethylene oxide in its Ninth Annual Report. For the reasons set forth in the attached comments, EOIC opposes classification of ethylene oxide as a known carcinogen. Neither the epidemiologic data nor genetic toxicity data support such a hazard classification.

If you have any questions regarding the enclosed comments, please contact Kathleen Roberts, Manager of the EOIC, at 703-741-5613.

Sincerely yours,

Enclosures



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COMMENTS ON
NATIONAL TOXICOLOGY PROGRAM
PROPOSED CLASSIFICATION OF ETHYLENE OXIDE
63 Fed. Reg. 5565 (February 3, 1998)

SUBMITTED BY

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Of The
Chemical Manufacturers Association

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March 23, 1998

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**COMMENTS OF THE ETHYLENE OXIDE INDUSTRY COUNCIL
NATIONAL TOXICOLOGY PROGRAM
PROPOSED CLASSIFICATION OF ETHYLENE OXIDE
NINTH ANNUAL REPORT**

EXECUTIVE SUMMARY

The Chemical Manufacturers Association Ethylene Oxide Industry Council (EOIC) is pleased to submit these comments on the National Toxicology Program's (NTP's) proposal to reclassify ethylene oxide (EO) to the "Known Carcinogen" category. 63 Fed. Reg. 5565 (February 3, 1998). EOIC members account for essentially all of domestic production of ethylene oxide and include a broad spectrum of ethylene oxide users in applications such as sterilizers, ethoxylators, and manufacturers of food, pharmaceutical, cosmetic, medical, and health products.¹

The EOIC is opposed to NTP's proposal to upgrade EO in the Ninth Annual Report on Carcinogens to the Known Carcinogen category. In the Federal Register notice, NTP indicated that it would base its proposed change on the recent classification of EO as a Category 1 carcinogen by the International Agency for Research on Cancer (IARC). EOIC believes that IARC's reclassification and NTP's proposed reclassification are inappropriate. The available data on EO indicate that the NTP should continue its classification of EO as a probable carcinogen.

¹ EOIC members are: Shell Chemical Company; BASF Corporation; McCormick & Company, Inc.; Abbott Laboratories; AlliedSignal, Inc.; Condea Vista Company; Sun Company, Inc.; Occidental Chemical Corporation; ARCO Chemical Company; Huntsman Corporation; The Dow Chemical Company; Union Carbide Corporation; Celanese Ltd.; Valchem Corporation; Ethox Corporation; and Texas Eastman Company.

While mechanistic data can be relevant to cancer classification, the specific EO genetic toxicity data that influenced IARC's upgrade of EO to a Category 1 classification is of dubious relevance to predicting carcinogenicity. IARC itself conceded that the epidemiologic data that it relied on was insufficient to support a category 1 designation.²

As Dr. John Higginson (former chair of IARC) commented in his March 1994 letter to IARC questioning the “known” carcinogen conclusion: “The extension of the use of mechanisms [for] Group 1 utilizing a wide range of genotoxic and mutational data etc. carries a possible risk of utilizing tests, markers or other systems whose relevance and predictiveness for human cancer may be uncertain and where there may be legitimate scientific disagreement. Thus the new classification will depend on greater use of scientific judgment [when] evaluating the significance and relevance of laboratory data which may also conflict with the epidemiologic evidence.” In the case of EO, the epidemiologic data clearly does not support classification of EO as a known carcinogen.

No studies have demonstrated a direct relationship between cancer in humans and exposure indicators such as sister chromatid exchange (SCE), chromosomal aberration and hemoglobin adduct formation. The predictive relevance of these exposure indicator findings is unclear when, as discussed below, epidemiologic data, based on over 30,000 workers in 12 studies, indicate that EO does not cause an increase in mortality, in cancer overall or in brain, stomach, or pancreatic cancers which were reported in some animal or isolated human studies. The evidence related to leukemias and lymphoma reported in these epidemiology studies is inconclusive and requires additional follow-up. However, it is important to note that the workers

² Meeting of the IARC working group on some industrial chemicals, Meeting Reports, Scand. J. Work. Environ. Health 1994; 20:227-29.

in the epidemiologic studies were exposed at levels far greater than the levels showing genotoxic effects. Based on this epidemiologic evidence and on recent developments in interpretation of EO genetic toxicity data, EOIC is requesting that IARC reconsider its Category 1 classification of EO and likewise requests that NTP reconsider its proposal to reclassify EO as a known carcinogen. EOIC's Petition to IARC will cite recent data not available in 1994 that show that the DNA damage that could lead to mutations, SCEs and chromosomal aberrations including micronuclei will repair even in workers who were highly exposed to EO or chronically exposed.

A. The Genetic Toxicity Data For EO Have Not Been Demonstrated and Would Not Be Expected to Be Predictive of Carcinogenicity

In 1994, IARC classified EO as a Group 1 carcinogen. In regards to its consideration of EO, the IARC working group reported: "Exceptionally, an agent (mixture) may be placed in Group 1 when evidence in humans is less than sufficient but there is sufficient evidence of carcinogenicity in animals and strong evidence in exposed humans that the agent (mixture) acts through a relevant mechanism of carcinogenicity."³ IARC's classification of EO marked "the first time that an agent was classified as category 1 in the absence of sufficient evidence of carcinogenicity from epidemiologic studies of cancer in humans."⁴

1. SCEs Are Biomarkers of Exposure and Have Not Been Demonstrated to Be Predictive of Carcinogenicity

Both *in vitro* and *in vivo* studies of EO have detected positive responses for a number of genetic endpoints. These include point mutations, sister chromatid exchanges, chromosomal aberrations, micronuclei, DNA adducts and hemoglobin adducts. The predictive

³ Meeting of the IARC working group on some industrial chemicals, Meeting Reports, Scand. J. Work. Environ. Health 1994; 20:227-29.

⁴ Letter from IARC Director P. Kleiheus to EOIC dated May 9, 1994.

relevance of any of these data to cancer hazard assessment has not been demonstrated. SCEs are a genotoxic, not a mutagenic, end point. Genotoxic effects like sister chromatid exchange or certain adduct counts are biomarkers indicative of recent EO exposure. No studies have described relationships between SCE changes and adverse health effects in humans. It is regarded as unlikely that SCE is directly related to development of a disease.⁵

There is no systematic relationship between the measured genetic or macromolecular endpoints and the onset or development of malignant disease in the extensive rodent studies that have been conducted. Stolley *et al.*⁶ commented that the health-related effects of the chromosome changes induced by EO are unknown. No studies have described relationships between SCE changes and adverse health effects in humans on an individual basis or on groups with similar exposures. More recently, Schulte *et al.*⁷ also concluded that it is not known whether increases in SCE are indicative of an increased risk of disease.

There are no data for EO in either experimental animals or humans that demonstrate that genetic toxicity endpoints have clear biologic significance or are precursors to tumors. For example the peripheral lymphocytes used in cytogenetic monitoring studies are terminally differentiated cells and thus are not involved in tumor formation. Other factors are known to influence the onset of carcinogenicity, e.g., the rate of formation of critical mutations and the repair of DNA damage. The critical mutations are not known in this case. Further, it is

⁵ Preston, J. Short/Medium Term Carcinogenicity Tests and Genetic and Related Effects, IARC Meeting - Lyon, France, October 1997 (In Press). A copy of this paper is attached.

⁶ Stolley, P.D. Sister-chromatid exchanges in association with occupational exposure to ethylene oxide. Mutation Research, 1984; 129:89-102.

⁷ Schulte, P.A. Biologic markers in hospital workers exposed to low levels of ethylene oxide. Mutation Research, 1992; 278: 237-51.

not known how the frequency of critical mutations or DNA repair following EO exposure compare in the experimental animals and in humans.

2. Incorporating Human Cytogenetic Data: DNA Repair and *In Vitro* Culture

In contrast to *in vitro* data, EO is not a potent carcinogen *in vivo*. From the viewpoint of hazard identification, it is important to recognize that for the great majority of chemicals, it is necessary for DNA replication to convert adducted DNA into mutations and chromosome aberrations via a process of fixation. For the types of chromosome alterations analyzed to date this replication occurs *in vitro* during the culturing of lymphocytes. The longer the time available for DNA repair to occur prior to DNA replication, the lower the probability of inducing a chromosomal alteration. Dr. Julian Preston of CIIT has described this phenomenon as a "race between repair and replication."⁸ Something seems to happen in the test tube that does not happen in humans. It is unlikely that one can show from *in vitro* experiments what amount of damage, induced over a period of time prior to taking a blood sample, would remain in the lymphocyte available to be converted into a genetic alteration at the time of DNA replication. Because there is continuing repair, one cannot look at DNA damage induced 10 years prior to taking a blood sample and find that damage converted into a chromosomal alteration. Indeed, if one treats human lymphocytes with a very potent alkylating agent, the DNA damage is sufficiently repaired within 48 hours so that chromosomal damage is not evident following the necessary *in vitro* culture of lymphocytes. The situation would be significantly obviated by using

⁸ See attached Preston presentation to IARC meeting; see also Preston, R.J., Fennell, T.R., Leber, A.P., Sielken, R.L. Jr., and Swenberg, J.A., Reconsideration of the Genetic Risk Assessment for Ethylene Oxide Exposures. Environ. Mol. Mutagen., 1995; 26:109-202.

fluorescent *in situ* hybridization methods in the analysis of transmissible aberrations induced directly in lymphocyte precursor cells.

A 1995 study by Tates *et al.*, examined peripheral blood from workers for a chemical manufacturing plant in the Netherlands.⁹ Workers were accidentally exposed to high doses of EO ranging from 52 to 785 mg/m³. Blood samples were collected from these workers 89-180 days after the accidental exposure. The authors find:

The genetic tests for group 1 workers were performed on blood samples collected 89-180 days after the incidental exposure. The absence of enhanced frequencies of mutations, micronuclei and SCEs suggests that significant induction of *hprt* mutations *in vivo* did not occur and that persistent preclastogenic lesions were not present in significant amounts when the exposed lymphocytes were put in culture to visualize any induced cytogenetic damage. This finding implies that the incidental exposure to high concentrations of EtO did not cause any measurable permanent mutational/cytogenetic damage in exposed lymphocytes.

In studies involving rodents and humans, there is repair of the DNA damage leading to *hprt* mutations:

Furthermore, the studies with adult rats and mice have indicated that the mutagenic effect of high acute doses of EtO is difficult to demonstrate because most premutagenic lesions will be repaired before mutation fixation can take place. In the present study, the premutagenic lesions induced by the high accidental exposure to EtO were apparently efficiently repaired before measurable mutation fixation could occur.

Induction of micronuclei could not be demonstrated in these highly exposed workers apparently due to the repair phenomenon:

⁹ A.D. Tates *et al.*, Biological Effect Monitoring in Industrial Workers Following Incidental Exposure to High Concentrations of Ethylene Oxide. *Mut. Res.*, 1995; 329: 63-67.

...[T]he blood samples for the measurement of micronuclei became available to us 89-180 days after the accident. Apparently, during such a long time interval between exposure and blood sample collection the preclastogenic lesions had already been repaired when exposed lymphocytes were put in culture. Thus, when such cells were undergoing their first *in vitro* DNA synthesis after the incidental exposure there were apparently negligible amounts of preclastogenic lesions present that could be fixed and converted into micronuclei. It is very reassuring to find that lymphocytes -- in case of incidental high exposures -- can very effectively remove preclastogenic damage.

Similarly, induction of SCEs could not be demonstrated in the high exposed workers. Again the authors attribute this finding to a cell repair phenomenon.

In other words, EtO induced DNA lesions in group 1 workers that could potentially induce SCEs were effectively repaired during the time interval (3-6 months) between accidental exposure to EtO and the culturing of lymphocytes for the demonstration of SCEs.¹⁰

3. Population Monitoring Studies Conducted on EO Are Too Small to Rule Out Confounding Effects

IARC's classification of EO as a Group 1 human carcinogen, reflected data on the cytogenetic analysis of peripheral lymphocytes in persons exposed to EO. However, from an epidemiologic perspective, use of such data is problematic. There are many confounders which can produce the effect of chromosomal aberrations. The EO population monitoring studies have insufficient size to rule out confounders with a reasonable degree of confidence. The EO cytogenetic population monitoring studies as presently conducted are difficult to interpret. The primary concerns include inability of the choice and size of populations to accurately account for known and unknown confounders; an analysis of inappropriate endpoints (chromatid-type

¹⁰ The Tates study also included workers with chronic exposure to low levels of EO; here, too, the authors concluded that there was no measurable permanent cytogenetic or mutational damage.

aberrations and SCEs); and an inappropriate extrapolation from peripheral lymphocyte data to predicted effects in the target organs for cancer.

Other studies not available to IARC in 1994 point out the role of confounders in EO studies. Monitoring of HEV levels in low-level exposure studies is in particular confounded by smoking habits which make results difficult to interpret.¹¹ IARC has recognized with respect to classification of other agents (e.g., styrene) that genetic population monitoring data are subject to significant limitations.

As noted above, the cytogenic analyses of lymphocytes potentially exposed *in vivo* following *in vitro* culture do not measure damage done by past exposure: they do not measure what they are intended to measure. In addition, it is inappropriate to attribute a cause and effect relationship to events which may be incidental or unrelated to the real carcinogenic process. Until the impact of these genetic effects is known, and tools are developed to measure them in response to relevant times of exposure, it is premature to attribute carcinogenic properties to them.

The lack of consistency between routes of exposure and animal species for tumor production in the EO cancer studies emphasizes that interaction with DNA is not the only factor that can determine a carcinogenic response. For example, when EO is given by mouth or injection, the only tumors observed are localized to the administration site. In inhalation studies, there are no nasal tumors or lung tumors in rats. The tumor responses in mice and rats are very different. In mice there was no leukemia response (although there was an increase in lymphoma in the females), but in the F344 rat, there was an increase of leukemias. Leukemia is a very

¹¹ Angerer, *et al.*, Int. Arch. Occup. Environ. Health, 1998; 71:14-18; Bader *et al.*, Int. Arch. Occup. Environ. Health, 1995; 67:237-242.

commonly occurring tumor in this type of rat; background rates may play an important part in the response. Although DNA adduct levels are similar in most tissues in each species, currently there is no understanding of why some tissues respond while others do not. Thus, it is difficult to define the relevant mode of action.

In summary, the genetic toxicity data on EO do not measure what they are supposed to measure -- effects of past levels of exposure -- and do not measure endpoints relevant to predicting cancer risk. It is highly speculative to infer cancer hazard from these data.

B. EO Epidemiologic Data Remains "Limited" and Insufficient to Justify the Known Carcinogen Classification

As EPA and other agencies have recognized, human epidemiology presents the most relevant evidence on risk,¹² particularly with a database as rich as for EO. EO is a well studied chemical with an unprecedented amount of published human epidemiology relating to it.¹³

Shore *et al.* conducted a comprehensive review of ten cohort studies that were available in 1993 primarily to consider leukemia, non-Hodgkin's lymphoma, stomach cancer, pancreatic cancer, and cancer of the brain and nervous system. Shore *et al.* evaluated magnitude

¹² As EPA observed in its Proposed Guidelines for Cancer Risk Assessment, 61 Fed. Reg. 17960, 17972-73 (April 23, 1996):

Epidemiologic data are extremely useful in risk assessment because they provide direct evidence that a substance produces cancer in humans, thereby avoiding the problem of species to species inference. Thus, when available human data are extensive and of good quality, they are generally preferable over animal data and should be given greater weight in hazard characterization and dose response assessment, although both are utilized.

¹³ The results of these studies have been summarized in a meta-analysis by Dr. Roy Shore, Ethylene Oxide: An Assessment of the Epidemiologic Evidence in Carcinogenicity. Brit. J. Ind. Med. 1993; 50:971-997.

and consistency of SMRs for the individual and combined studies, as well as trends by intensity or frequency of exposure, duration and latency. The potential for confounding by other workplace chemicals was carefully considered.¹⁴ The meta-analysis provides important in-depth analysis of the significance of the Hogstedt studies and the NIOSH studies including discussion of the relevance of exposure data and other critical issues for evaluation of unresolved questions related to leukemia and non-Hodgkin's lymphoma.

¹⁴ The Shore abstract concludes:

Three small studies by Hogstedt initially suggested an association between EtO and leukemia, but in seven subsequent studies the SMRs for leukemia have been much lower. For the combined studies the SMR = 1.06 (95% confidence interval (95% CI) 0.73-1.48). There was a slight suggestion of a trend by duration of exposure ($p = 0.19$) and a suggested increase with longer latency ($p = 0.07$), but there was no overall trend in risk of leukemia by intensity or frequency of exposure; nor did a cumulative exposure analysis in the largest study indicate a quantitative association. There was also an indication that in two studies with increased risks the workers had been exposed to other potential carcinogens. For non-Hodgkin's lymphoma there was a suggestive risk overall (SMR = 1.35, 95% CI 0.93-1.90). Breakdowns by exposure intensity or frequency, exposure duration, or latency did not indicate an association, but a positive trend by cumulative exposure ($p = 0.05$) was seen in the largest study. There was a suggested increase in the overall SMR for stomach cancer (SMR = 1.28, 95% CI 0.98-1.65 (CI 0.73-2.26 when heterogeneity among the risk estimates was taken into account)), but analyses by intensity or duration of exposure or cumulative exposure did not support a causal association for stomach cancer. The overall SMRs and exposure-response analyses did not indicate a risk from EtO for pancreatic cancer (SMR = 0.98), brain and nervous system cancer (SMR = 0.89), or total cancer (SMR = 0.94). Although the current data do not provide consistent and convincing evidence that EtO causes leukemia or non-Hodgkin's lymphoma, the issues are not resolved and await further studies of exposed populations.

In a hazard characterization of epidemiologic data presented in December 1997 to the Society of Risk Analysis, Dr. Teta updated the Shore EO meta-analysis to include the two studies that have become available more recently.¹⁵ (A copy of Dr. Teta's and Dr. Sielken's presentations to the Society for Risk Analysis is attached.) To date, mortality from cancer among workers exposed to EO has been studied in 12 distinct cohorts that include over 33,000 workers and more than 800 cancers. These studies include a large scale mortality study by U.S. NIOSH.¹⁶ An objective conclusion from these studies is that EO does not cause an increase in mortality, cancer overall, or brain, stomach, or pancreatic cancers that were reported in some animal or isolated human studies. Evidence as to leukemias and lymphomas is inconclusive and requires additional follow-up.

The observed to expected ratio for all cancers combined is not in excess (SMR=0.94). For all of the cancers of *a priori* interest, the SMRs do not differ statistically (at the 5% level of significance) from 1.0. The SMR for leukemia decreases to less than 1.0 when the Hogstedt study is excluded.¹⁷ There are no statistically significant positive trends with

¹⁵ Since Shore's meta-analysis, two additional studies have been completed (an update by Hagmar of his Swedish sterilizer group and a study by Olsen of Dow ethylene chlorohydrin workers). Hagmar *et al.* Cancer Incidence In Sterilant Workers Exposed To Ethylene Oxide. Occup. Environ Med., 1995; 52: 154-6; Olsen *et al.* Mortality From Pancreatic and Lymphopoietic Cancer Among Workers in Ethylene and Propylene Chlorohydrin Production, Occup. Environ Med., 1997; 592-598.

¹⁶ Steenland, K., Stayner, L., Greife, A., Halperin, W., Hayes, R., Hornung, R., Nowlin, S. Mortality among workers exposed to ethylene oxide. N. Eng. J. Med., 1991;324: 1402-7; Stayner, L., Steenland, K., Greife, A., Hornung, R., Hayes, R., Nowlin, S., *et al.* (1993). Exposure-response analysis of cancer mortality in a cohort of workers exposed to ethylene oxide. Am. J. Epidemiol., 1993;138: 787-98.

¹⁷ Statistical studies for heterogeneity identify the Hogstedt study as anomalous. See Shore's meta-analysis for a discussion of potential confounders in the Hogstedt study.

duration, intensity or latency, with the exception of brain cancer.¹⁸ Although there is not a positive trend with latency for leukemia, there are more cases than expected in the longest latency category. The meta-SMR for non Hodgkin's lymphoma is moderately increased (1.34) and of borderline statistical significance, but there are no positive trends with duration, intensity or latency.

Stayner *et al.* conducted additional statistical analyses of workers from 13 of the 14 medical products/spice plants included in the NIOSH mortality study. Both stratified (SMR life table approach) and multivariate modeling (Cox Proportional Hazards) were used. A non-standard group of lymphohematopoietic tissue cancers was used in which lymphocytic leukemia and non-Hodgkins lymphoma (NHL) were combined into a category called "lymphoid" tumors.

The stratified analyses did not indicate any positive trends between exposure and cancer (stomach, kidney, pancreas, brain leukemia, NHL) for any exposure metric. Using the regression model, with cumulative EO dose entered as a continuous variable, the authors report: (1) a statistically significant association with "lymphoid" cancers, (2) a weaker non-statistically significant association with NHL and leukemia and (3) inverse relationships with stomach, kidney and brain cancers. There were no notable findings in the analyses for the other exposure metrics.¹⁹

¹⁸ The trend with latency was based on only 4 studies which provided brain cancer data by time since first exposure. The meta-SMR for brain cancer is not increased (0.96) based on 7 studies that reported results for this cause. It is highly likely that brain cancer rates were not increased for the 5 studies not reporting results for this type of cancer and that the meta-SMR would be even smaller if these data were included.

¹⁹ Four exposure metrics were examined: cumulative, duration, average and maximum.

The authors discuss the limitation of their analyses, specifically the impact of a few highly exposed cases in the regression approach. Such cases have less impact in the stratified analyses. (One such case was estimated to have 1,356 ppm/year EO exposure.) Exclusion of the one extreme case resulted in a risk estimate for “lymphoid” tumors of similar magnitude, but it was no longer statistically significant. No explanation is provided for the inverse relationship between exposure and lymphohematopoietic cancers in women.

For EO, as for most chemicals, the potential occupational exposures, now and in the past, are significantly higher than environmental exposures. The current OSHA permissible exposure limit for EO is 1 ppm TWA, adopted in 1984. Previously, exposure levels were much higher. For example, in the 1960's, industrial exposures ranged from 3-20 ppm TWA, with operator concentration exposures estimated at between 5-10 ppm TWA as an eight hour average.²⁰ In the early period odor was detected, suggesting that exposures may have reached hundreds of ppm. The fact that there is no excess cancer overall or excesses of stomach, pancreatic, brain, and nervous system cancers and equivocal findings related to leukemia and lymphoma in the large cohort of workers is relevant to hazard assessment. These findings suggest that the animal carcinogenicity of EO and assumptions about the relevance of EO genetic toxicity data are not borne out by the weak epidemiologic evidence.

At its February 1998 meeting, IARC recognized with respect to acrylonitrile -- another multi-site animal carcinogen -- that a “possible” rather than “probable” classification was appropriate where extensive epidemiologic evidence suggested a lower classification. Similarly,

²⁰ Teta *et al.* Mortality Study of Ethylene Oxide Workers in Chemical Manufacturing: A Ten Year Update. Br. J. Ind. Med. 1993; 50(8): 704-9.

the epidemiologic evidence on EO supports a “probable classification” because the extensive epidemiologic data does not show tumor incidence suggested by rodent tests.

CONCLUSION

Given the questionable relevance of the specific EO genetic toxicity data to predicting carcinogenicity and the strength of evidence from the epidemiology studies, EOIC recommends that NTP does not list EO as a “known carcinogen” in the ninth annual report, but continues to categorize it as a “probable carcinogen.”

Attachments (2)

**Cancer Dose-Response Assessment of Ethylene Oxide
Based on Animal and Human Data**

**Session:
Recent Ethylene Oxide Research
and Its Implications for Risk Assessment**

**Society for Risk Analysis
Annual Meeting and Exposition
Capital Hilton
Washington, D.C.**

December 8, 1997

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Incorporating
More Science
and
More of the Available Data
into the
Dose-Response Assessment
of
Ethylene Oxide

Available Data from

**Several
Human Epidemiological Studies
and Animal Bioassays**

and

Several Different Cancer Endpoints

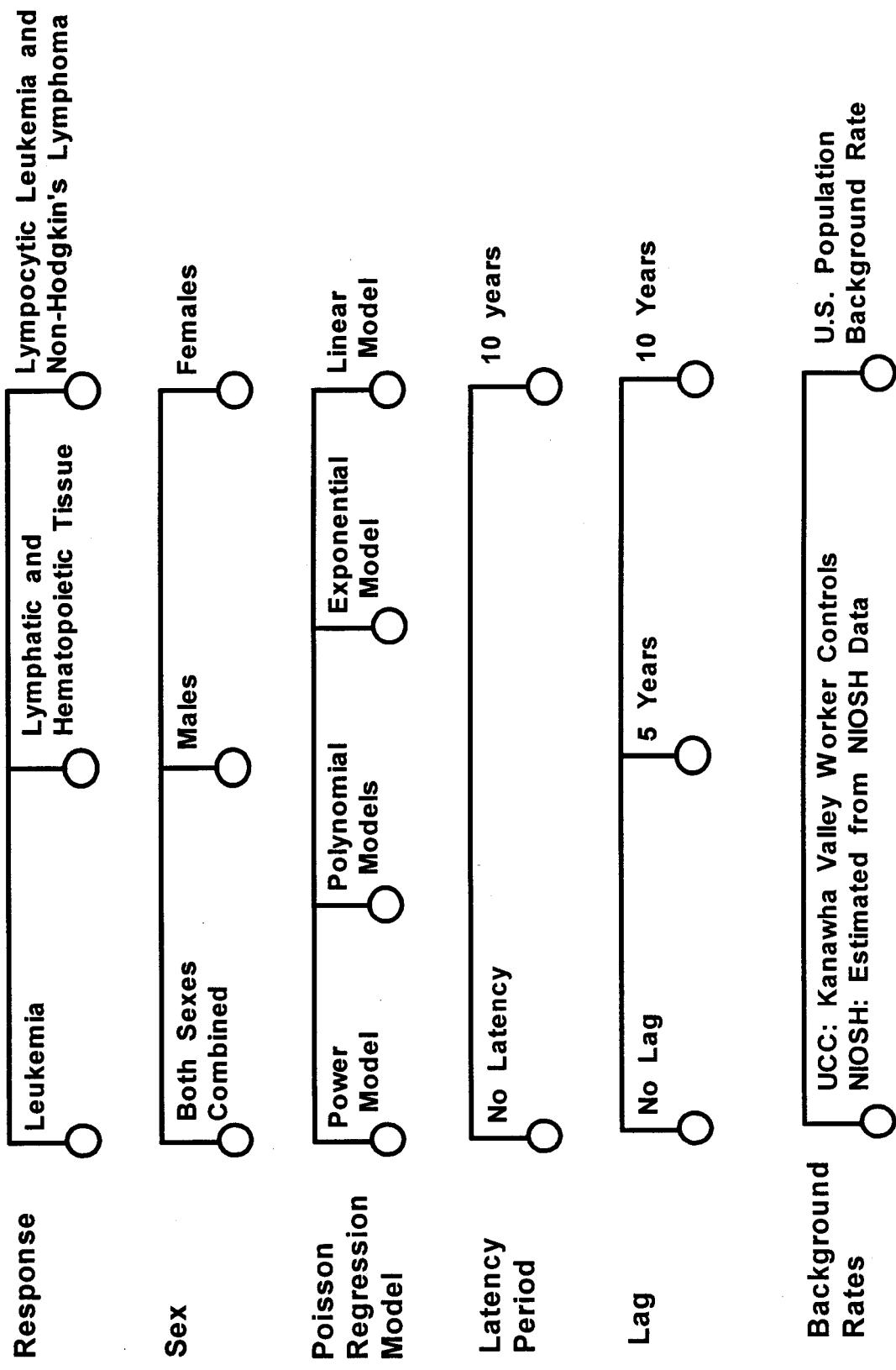
Human Epidemiological Data:

Union Carbide Corporation (UCC) Epidemiological Study of Ethylene Oxide Workers in Chemical Manufacturing

Human Epidemiological Data:

**NIOSH Epidemiological Study
of
Exposed Workers
in the Sterilant Industry**

Tree for the UCC and NIOSH Epidemiological Data Analyses



NIOSH Epidemiological Data

PERSON YEARS (Number of Leukemia Deaths)

Dose Interval (ppm-years)	ALL	MALES	FEMALES
(0, 33]	(17,443 Workers)	(7,586 Workers)	(9,857 Workers)
0	7,401.8 (0)	2,679.5 (0)	4,722.3 (0)
(33, 125]	234,083.6 (8)	91,281.6 (4)	142,802.1 (4)
(125, 285]	39,142.3 (1)	20,403.4 (0)	18,739.0 (1)
(285, ∞)	10,168.8 (1)	6,827.4 (1)	3,341.4 (0)
Total Person-Years	294,172.5	123,883.9	170,288.6

NIOSH Epidemiological Data

PERSON YEARS (Number of Lymphatic and Hematopoietic Deaths)

Dose Interval (ppm-years)	ALL	MALES	FEMALES
(17,443 Workers)	(7,586 Workers)	(9,857 Workers)	
0	7,401.8 (0)	2,679.5 (0)	4,722.3 (0)
(0, 33]	234,083.6 (21)	91,281.6 (13)	142,802.1 (8)
(33, 125]	39,142.3 (4)	20,403.4 (3)	18,739.0 (1)
(125, 285]	10,168.8 (4)	6,827.4 (4)	3,341.4 (0)
(285, ∞)	3,376.0 (4)	2,692.1 (4)	683.9 (0)
Total Person-Years	294,172.5	123,883.9	170,288.6

NIOSH Epidemiological Data

**PERSON YEARS (Number of Lymphocytic Leukemia
and Non-Hodgkin's Lymphoma Deaths Combined)**

Dose Interval (ppm-years)	ALL	MALES	FEMALES
(17,443 Workers)	(7,586 Workers)	(9,857 Workers)	
0	7,401.8 (0)	2,679.5 (0)	4,722.3 (0)
(0, 33]	234,083.6 (8)	91,281.6 (6)	142,802.1 (2)
(33, 125]	39,142.3 (3)	20,403.4 (2)	18,739.0 (1)
(125, 285]	10,168.8 (3)	6,827.4 (3)	3,341.4 (0)
(285, ∞)	3,376.0 (3)	2,692.1 (3)	683.9 (0)
Total Person-Years	294,172.5	123,883.9	170,288.6

The modeling and other analyses of the NIOSH data include only person-years at risk.

Because entry into the NIOSH data set was restricted to workers with positive cumulative exposure to ethylene oxide, the modeling and other analyses include only person-years with positive cumulative exposure to ethylene oxide.

EO Exposure History

UCC EO Manufacturing Operations Average 8 hour TWA's (ppm)		Average in Medium Exposure Jobs	Average in Higher Exposure Jobs
Exposure Period	Average in Lower Exposure Jobs		
1925 to 1939	14	28	70
1940 to 1956	7	14	21
1957 to 1973	5	7.5	10
1974 to 1978	0.3	0.65	1

Peaks much higher (e.g., > 400 - 700 ppm in early years)

UCC Response Tables

PERSON YEARS
 (Number of Leukemia Deaths)

Dose Interval (ppm-years)	MALES (26,952 Controls + 1,896 Exposed Workers)
0	859,858.0 (80)
(0, 33]	30,266.6 (2)
(33, 125]	12,911.4 (1)
(125, 285]	6,596.9 (1)
(285, ∞)	1,984.0 (1)
Total Person-Years	911,616.9

UCC Response Tables

PERSON YEARS
 (Number of Lymphocytic Leukemia
 and Non-Hodgkin's Lymphoma Deaths Combined)

Dose Interval (ppm-years)	MALES (26,952 Controls + 1,896 Exposed Workers)
0	859,858.0 (118)
(0, 33]	30,266.6 (2)
(33, 125]	12,911.4 (1)
(125, 285]	6,596.9 (0)
(285, ∞)	1,984.0 (0)
Total Person-Years	911,616.9

UCC Response Tables

PERSON YEARS
 (Number of Lymphatic
 and Hematopoietic Deaths)

Dose Interval (ppm-years)	MALES (26,952 Controls + 1,896 Exposed Workers)
0	859,858.0 (197)
(0, 33]	30,266.6 (3)
(33, 125]	12,911.4 (2)
(125, 285]	6,596.9 (1)
(285, ∞)	1,984.0 (1)
Total Person-Years	911,616.9

Leukemia Response Data

Focus on

Poisson Regression Analysis:

Form 1:

Mean Response Rate
in a Person-Year

$$= \text{Background Rate} \times \begin{array}{l} \text{Effect of Age} \\ \times \text{Effect of Calendar Year} \\ \times \text{Effect of Years Since Hire} \\ \times \text{Function (EO dose)} \end{array}$$

Years Since Hire

= Years Since Hire

**for workers not exposed to
ethylene oxide (controls)**

Years Since Hire

= Years Since First EO Exposure

**for workers exposed to
ethylene oxide**

Partitions used in the Poisson Regression Analysis of the UCC and NIOSH Epidemiological Data Sets

Form 1:

Mean Response Rate in a Person-Year

$$= [\text{Background Rate} \times \text{Effect of Age} \\ \times \text{Effect of Calendar Year} \\ \times \text{Effect of Years Since Hire}] \\ \times \text{Function (EO dose)}$$

Age Intervals:

$$\leq 50, > (50, 70], \text{ and } > 70$$

Calendar Year Intervals:

$$\leq 1939, (1939, 1956], (1956, 1973], \text{ and } > 1973$$

Year Since Hire Intervals:

$$\leq 10, \text{ and } > 10$$

Function (EO dose):

Function (EO ppm - years):

$$\text{Linear Model} = 1 + \beta_1 \times \text{Dose}$$

Polynomial Model:

$$\text{Linear \& Quadratic} = 1 + \beta_1 \times \text{Dose} + \beta_2 \times \text{Dose}^2$$

Polynomial Model:

$$\begin{aligned} \text{Linear \& Quadratic \& Cubic} \\ = 1 + \beta_1 \times \text{Dose} + \beta_2 \times \text{Dose}^2 + \beta_3 \times \text{Dose}^3 \end{aligned}$$

$$\text{Power Model} = 1 + \beta_1 \text{ Dose}^{\beta_2}$$

Results for Different

Latencies (0 or 10 years)

and Different

Lags (0, 5, or 10 years)

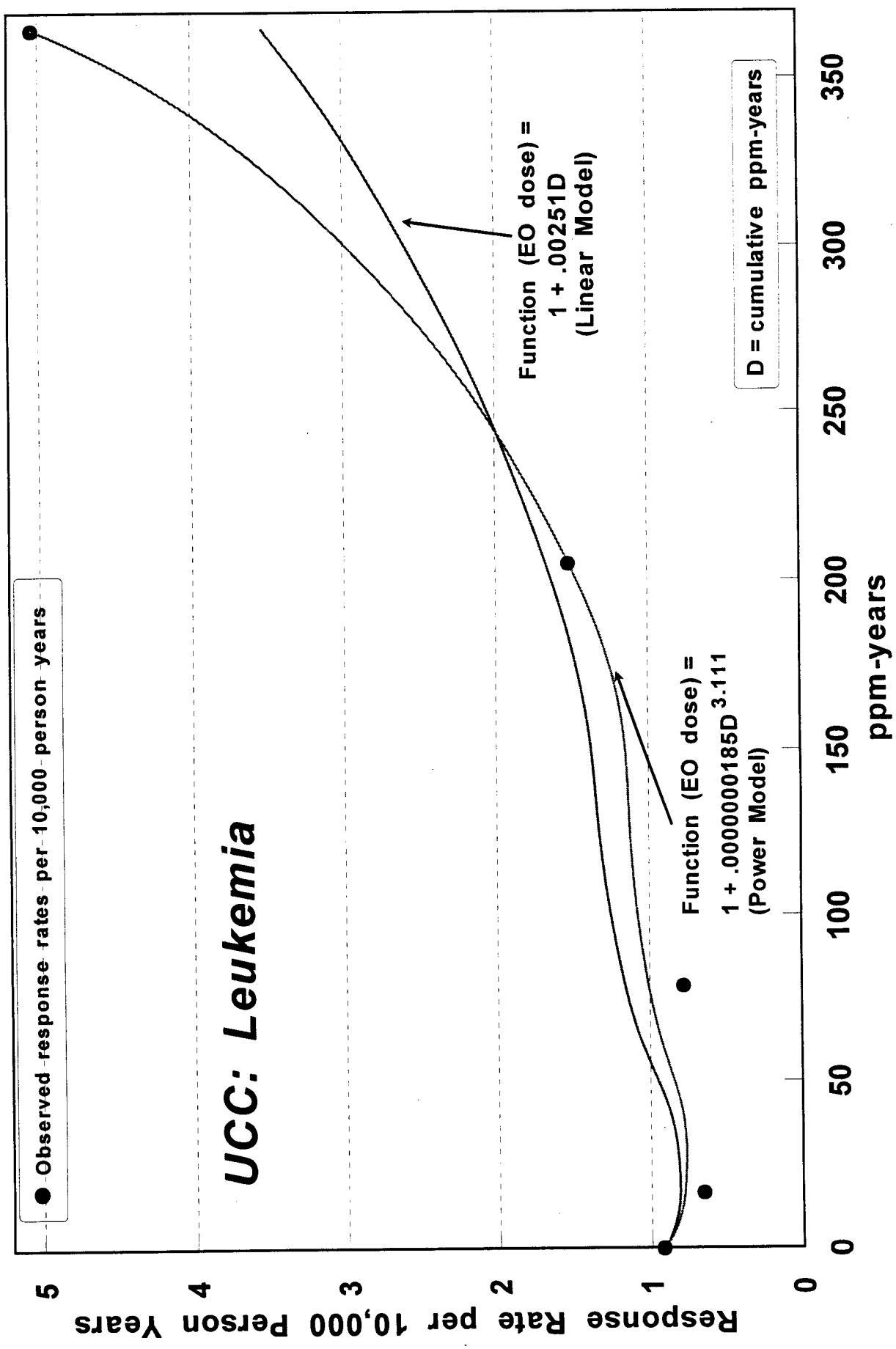
are Similar.

Results for

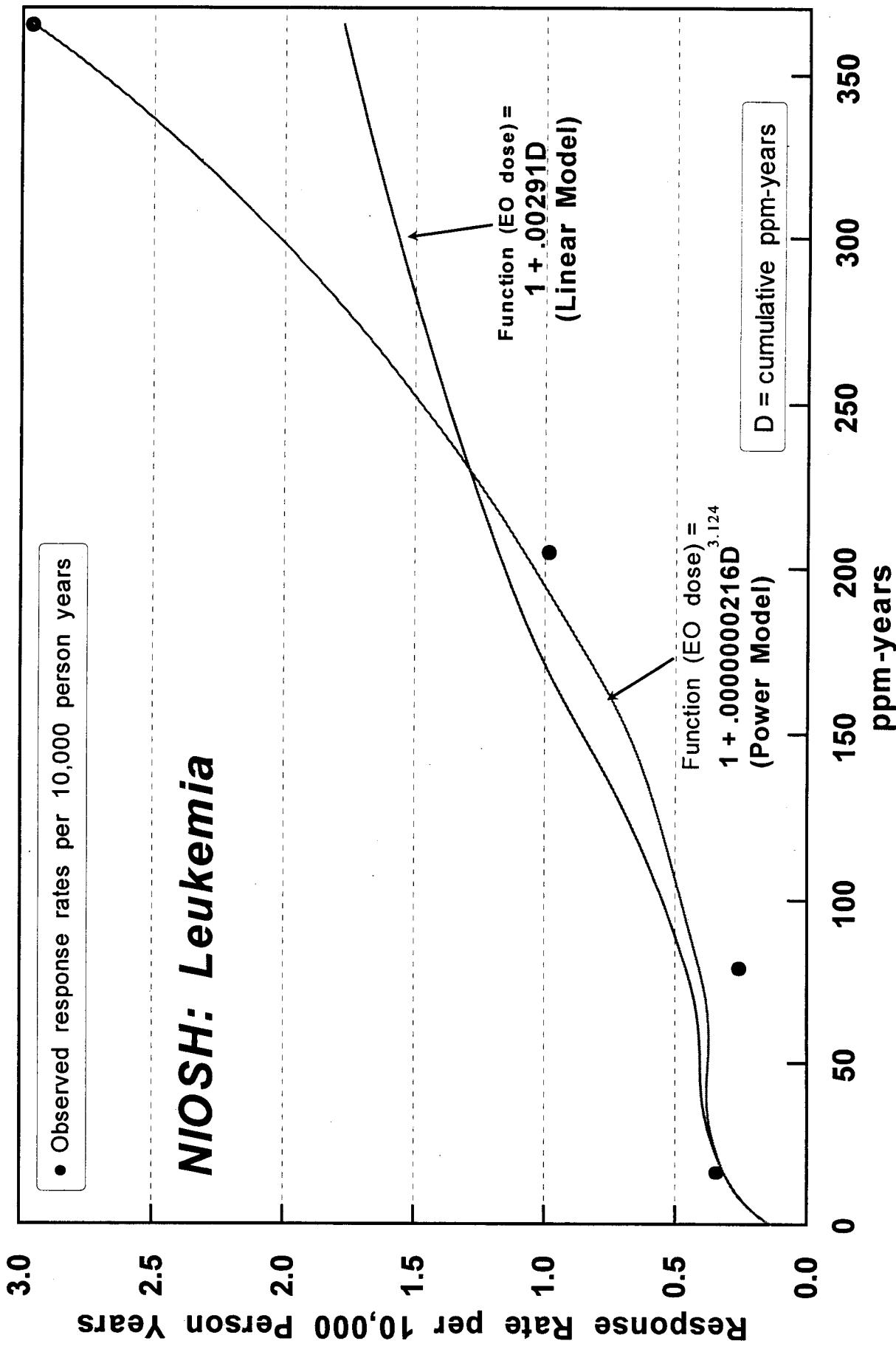
Latency = 0 years

Lag = 0 years

Observed and predicted leukemia response rates using Poisson regression analyses based on an estimated background leukemia hazard rate (incorporating covariates for age, calendar year, and years since hire) and different functional forms for the dose-dependent multiplicative effect of the age-dependent cumulative ethylene oxide exposure



Observed and predicted leukemia response rates using Poisson regression analyses based on an estimated background leukemia hazard rate (incorporating covariates for age, calendar year, and years since hire) and different functional forms for the dose-dependent multiplicative effect of the age-dependent cumulative ethylene oxide exposure



Nonparametric Estimates of the Dose-Response Relationship and Fitted Models

4

UCC: Leukemia
Latency = 0, Lag = 0

The size of the DOT (●) is proportional to the number of person-years. The DOT at 0 ppm-years should be huge (approximately 30 times the size of the DOT at 16.5 ppm-years).

3

Rate Ratio

2

1

0

$$1 + .00281D$$

$$1 + .000000697D^{2.901}$$

$$1 - .00403D + .0000263D^3$$

$$1 - .00403D + .0000263D^2$$

- nonparametric estimate D = ppm-years

0 50 100 150 200 250 300 350
ppm-years

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**The models
which BEST FIT
the Human Epidemiological Data
are the**

Polynomial Models

and the

Power Model.

**The fitted models
for the UCC data
are VERY SIMILAR
to the fitted models
for the NIOSH data.**

Fitted Power Model: UCC vs NIOSH

4

Leukemia
Latency = 0, Lag = 0

3

Rate Ratio

2

1

0

$$\text{NIOSH} = 1 + .00000000198D^{3.174}$$

$$\text{UCC} = 1 + .00000000697D^{2.901}$$

D = ppm-years

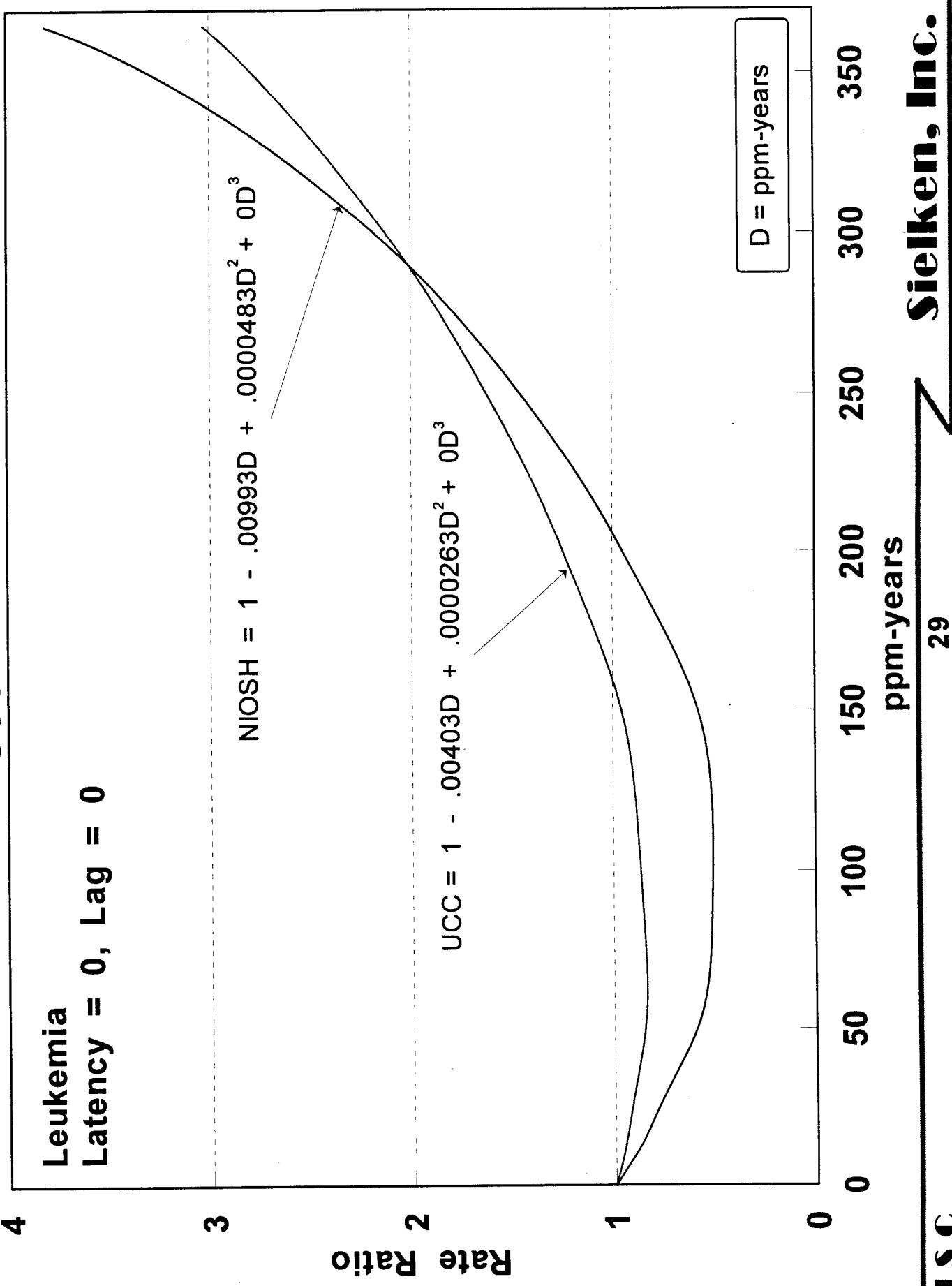
0 50 100 150 200 250 300 350
ppm-years

JSC

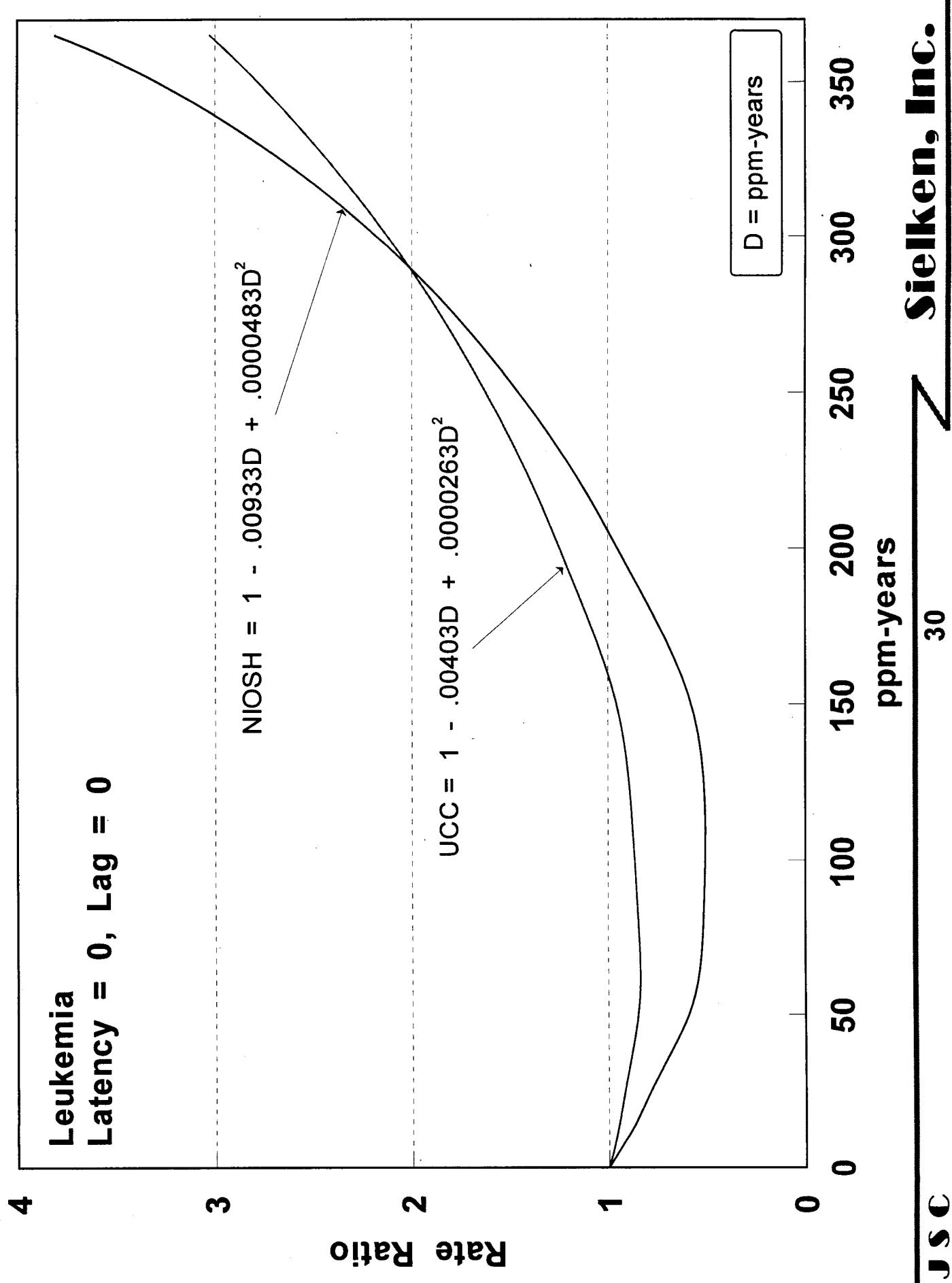
28

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Fitted Polynomial (Linear, Quadratic & Cubic) Model: UCC vs NIOSH



Fitted Polynomial (Linear & Quadratic) Model: UCC vs NIOSH



Fitted Linear Model: UCC vs NIOSH

4

Leukemia
Latency = 0, Lag = 0

3

Rate Ratio

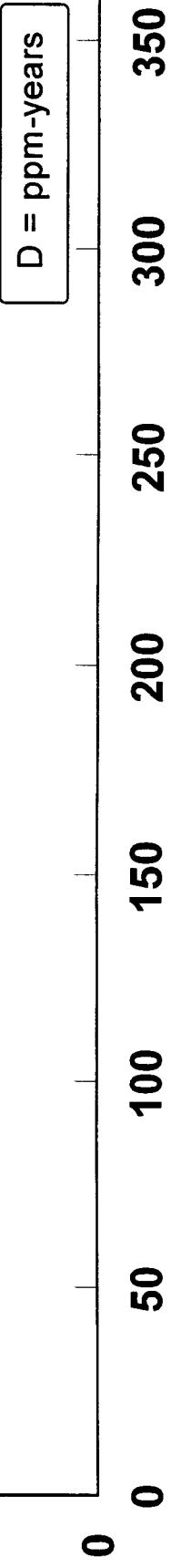
2

1

0

$$\text{NIOSH} = 1 + .00259D$$

$$\text{UCC} = 1 + .00281D$$



Basis for Added Cancer Risk Predictions

Mean Response Rate in a Person-Year
= [U.S. 1990 Age-Dependent
Background Leukemia Rate]
× Function (EO dose)

UCC data based predictions use
Function (EO dose)
estimated from UCC data.

NIOSH data based predictions use
Function (EO dose)
estimated from NIOSH data.

For any specific model,

**the Added Cancer Risk Predictions
for an Environmental Exposure
to 1 ppb for 70 years**

are VERY SIMILAR

for the UCC and NIOSH data sets.

**Added Cancer Risk Predictions
 (Poisson Regression Analysis: Form 1)
 Environmental Exposure to 1 ppb for 70 years**

Leukemia

Latency: 0 years, No Lag in Exposure

Model with Restricted Parameters	UCC data	NIOSH data
Power	3.7×10^{-12}	7.3×10^{-13}
Polynomial: Linear & Quadratic & Cubic	0.0	0.0
Polynomial: Linear & Quadratic	0.0	0.0
Linear	1.9×10^{-6}	1.8×10^{-6}

Risks Include U.S. 1990 Age-Dependent Competing Risks

Results for

Latency = 10 years

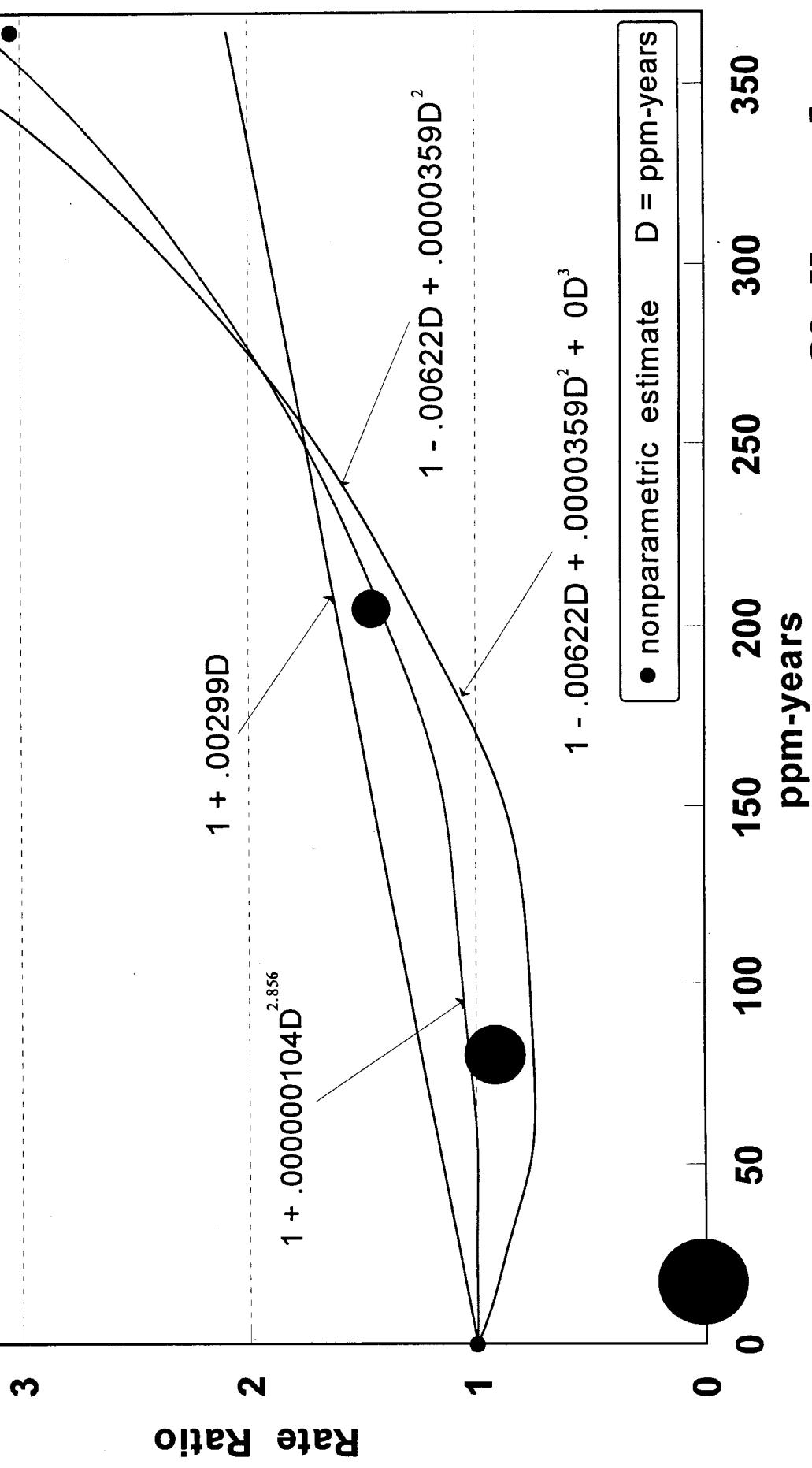
Lag = 5 years

Nonparametric Estimates of the Dose-Response Relationship and Fitted Models

4

UCC: Leukemia
Latency = 10, Lag = 5

The size of the DOT (●) is proportional to the number of person-years. The DOT at 0 ppm-years should be huge.



**The models
which BEST FIT
the Human Epidemiological Data
are the**

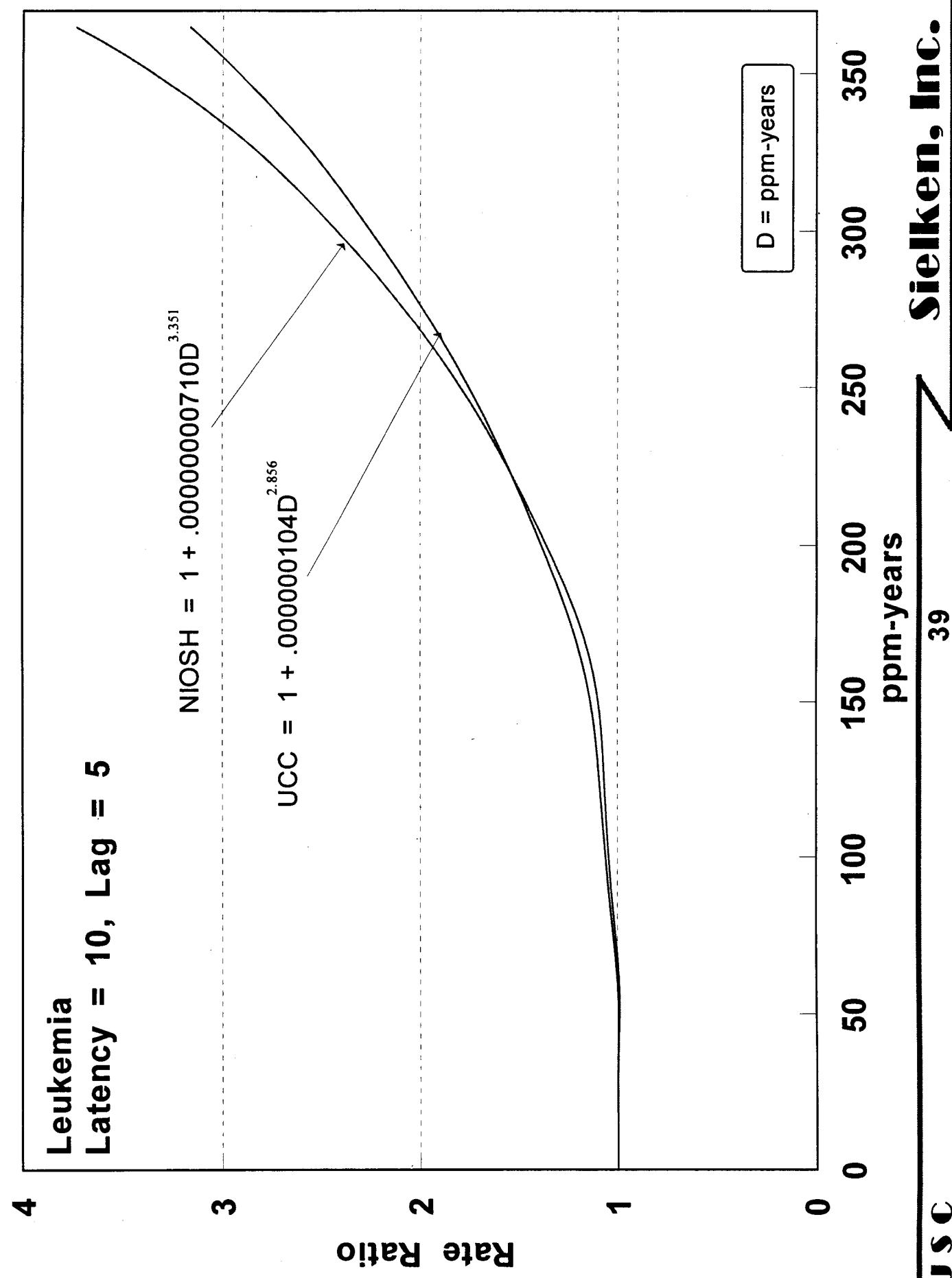
Polynomial Models

and the

Power Model.

**The fitted models
for the UCC data
are VERY SIMILAR
to the fitted models
for the NIOSH data.**

Fitted Power Model: UCC vs NIOSH



Fitted Polynomial (Linear, Quadratic & Cubic) Model: UCC vs NIOSH

4

Leukemia
Latency = 10, Lag = 5

3

Rate Ratio

1

0

$$\text{NIOSH} = 1 - .00827D + .0000421D^2 + 0D^3$$

$$\text{UCC} = 1 - .00622D + .0000359D^2 + 0D^3$$

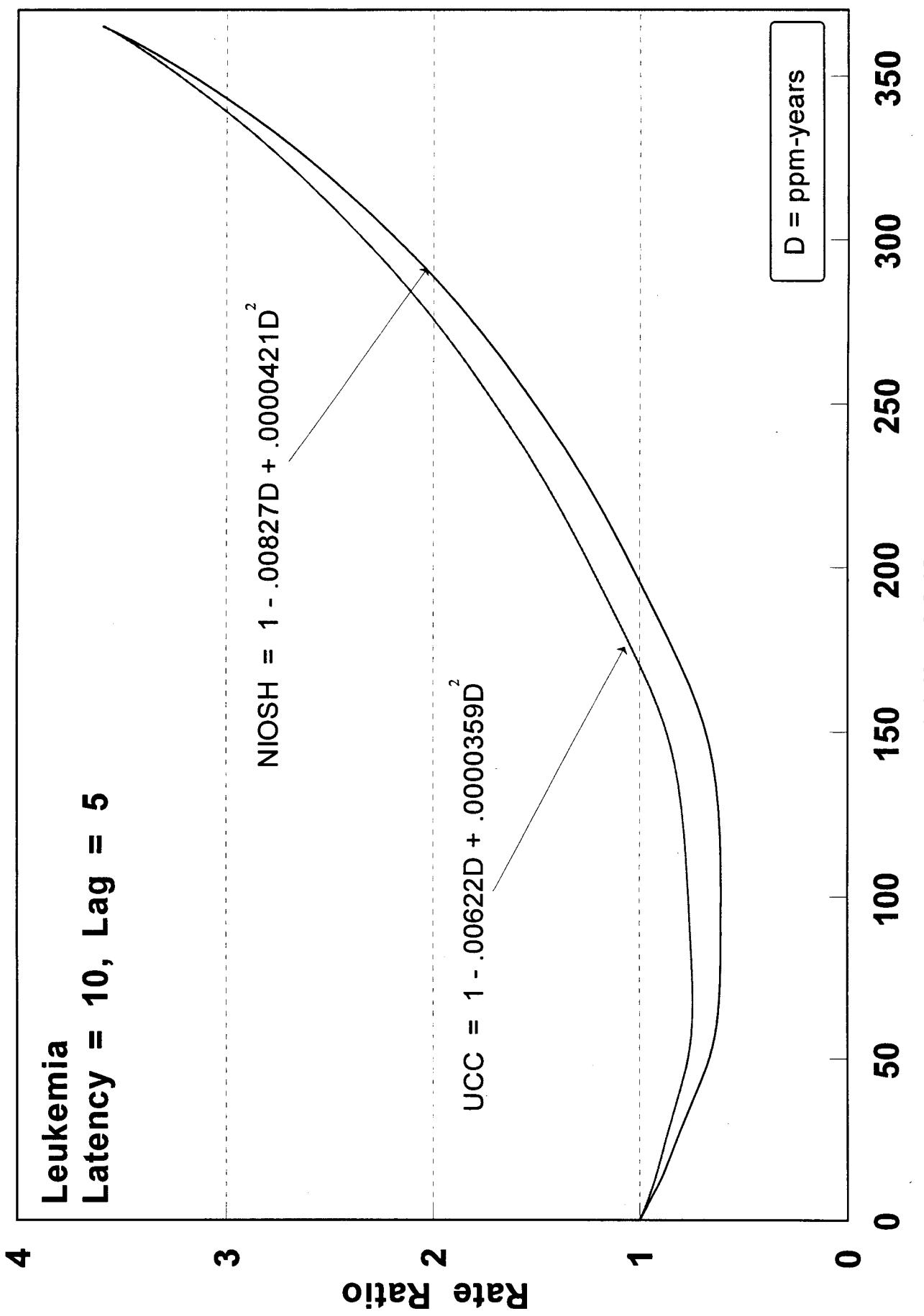
D = ppm-years

0 50 100 150 200 250 300 350
ppm-years

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Fitted Polynomial (Linear & Quadratic) Model: UCC vs NIOSH



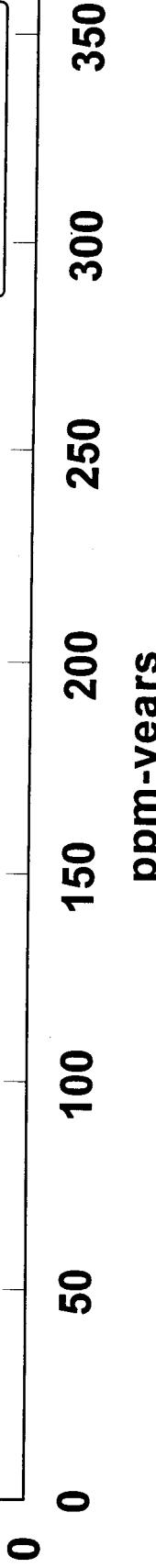
Fitted Linear Model: UCC vs NIOSH

Leukemia
Latency = 10, Lag = 5

$$\text{NIOSH} = 1 + .00319D$$

$$\text{UCC} = 1 + .00299D$$

D = ppm-years



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For any specific model,

**the Added Cancer Risk Predictions
for an Environmental Exposure
to 1 ppb for 70 years**

are VERY SIMILAR

for the UCC and NIOSH data sets.

**Added Cancer Risk Predictions
(Poisson Regression Analysis: Form 1)
Environmental Exposure to 1 ppb for 70 years**

Leukemia

Latency: 10 years, Lag = 5 years

Model with Restricted Parameters	UCC data	NIOSH data
Power	4.6×10^{-12}	1.6×10^{-13}
Polynomial: Linear & Quadratic & Cubic	0.0	0.0
Polynomial: Linear & Quadratic	0.0	0.0
Linear	1.8×10^{-6}	2.0×10^{-6}

Risks Include U.S. 1990 Age-Dependent Competing Risks

Margins of Exposure:

Determining the BENCHMARK RISK

ED_{10} , ED_{01} , ED_{005} , ED_{001} , etc.

Want EDx's to be mostly model invariant
(i.e., not varying appreciably from model to model)

-- this seems to be ED_{001} for Ethylene Oxide

Want EDx's to be from the heart of the observed data

-- this seems to be ED_{001} for Ethylene Oxide

Want dose-response modeling to satisfy
statistical goodness-of-fit criteria, etc.

Benchmark Doses (ppm) Environmental Exposure for 70 years

UCC Data: Leukemia
Latency = 10 years, Lag = 5 years

Model	ED ₀₀₁	ED ₀₀₅	ED ₀₁	ED ₁₀
Power	0.83	1.46	1.87	4.27
Polynomial (Linear & Quadratic & Cubic)	0.91	1.39	1.78	4.89
Polynomial (Linear & Quadratic)	0.91	1.39	1.78	4.89
Linear	0.54	2.73	5.48	58.11

Benchmark Doses (ppm) Environmental Exposure for 70 years

NIOSH Data: Leukemia
Latency = 10 years, Lag = 5 years

Model	ED ₀₀₁	ED ₀₀₅	ED ₀₁	ED ₁₀
Power	0.84	1.36	1.68	3.4
Polynomial (Linear & Quadratic & Cubic)	0.99	1.41	1.76	4.6
Polynomial (Linear & Quadratic)	0.99	1.41	1.76	4.6
Linear	0.51	2.56	5.14	54.38

The Benchmark Doses

ED_{001} , ED_{005} , ED_{01} , and ED_{10}

for the UCC data set
are **VERY SIMILAR**
to the corresponding
Benchmark Doses
for the NIOSH data set.

Among the Benchmark Doses

ED_{001} , ED_{005} , ED_{01} , and ED_{10}
the most model invariant
Benchmark Dose is

$$ED_{001}.$$

The range of ED_{001} values for environmental exposures
for 70 years over the different models is

0.54 to 0.91

for the UCC data and

0.51 to 0.99

for the NIOSH data.

The average of the ED₀₀₁ values for environmental exposures for 70 years for the different models and the UCC and NIOSH data sets is approximately

$$ED_{001} = 0.8 \text{ ppm.}$$

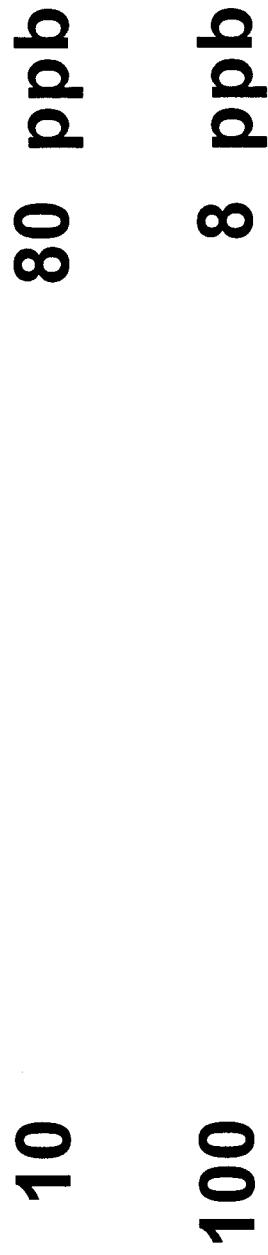
Margins of Exposure for Environmental Exposures

for 70 years:

Based on $ED_{001} = 0.8 \text{ ppm} = 800 \text{ ppb}$

Margin of Exposure

Concentration



For leukemia,

**the UCC and NIOSH
data sets yield**

approximately the same

Added Cancer Risk Predictions.

**For the Best Fitting
Poisson Regression Models
(the Polynomial and Power Models),**

**the Added Cancer Risk Prediction for
an Environmental Exposure
of 1 ppb for 70 years is less than**

$$1 \times 10^{-6}$$

If the basis for the
Added Cancer Risk Predictions
is

$$\begin{aligned} \text{Mean Response Rate} \\ = [\text{U.S. 1990 Population} \\ \quad \times \text{Background Leukemia Rate}] \\ \quad \times \text{Function (EO dose)}, \end{aligned}$$

then an alternative form of the Poisson
Regression Analysis is the following form
(Form 2) which uses the U.S. Background
Leukemia Rates in the estimation of the
Function (EO dose)
from the UCC and NIOSH data.

Poisson Regression Analyses:

Form 2:

Mean Response Rate in a Person-Year

$$\begin{aligned} &= [\text{U.S. Background Rate}] \\ &\quad \times \text{Healthy Worker Effect} \\ &+ [\text{U.S. Background Rate}] \\ &\quad \times \text{Function (EO dose)} \end{aligned}$$

Partitions used in the Poisson Regression Analysis of the UCC and NIOSH Epidemiological Data Set

Form 2:

Mean Response Rate in a Person-Year

$$\begin{aligned} &= [\text{US Background Rate}] \\ &\quad \times \text{Healthy Worker Effect} \\ &[\text{US Background Rate}] \\ &\quad \times \text{Function (EO dose)} \end{aligned}$$

Age Intervals in US Background Rate Data Tables:

≤ 20 , (20, 25], (25, 30], (30, 35], (35, 40],
(40, 45], (45, 50], (50, 55], (55, 60], (60, 65],
(65, 70], (70, 75], (75, 80], and > 80

Calendar Year Intervals in US Background Rate Data Tables:

≤ 1940 , (1940, 1950], (1950, 1960], (1960, 1970],
(1970, 1980], and > 1980

The Added Cancer Risk Predictions
are the same regardless of whether
the

Healthy Worker Effect

is modeled as
an additive effect
or
a multiplicative effect.

If

$$\text{Function (EO dose)} = 1 + \dots$$

then the added risk
for an additive healthy worker effect

$$\begin{aligned} & [\text{Rate}] \times \text{Healthy Worker Effect} \\ & + \\ & [\text{Rate}] \times \text{Function (EO dose)} \end{aligned}$$

is the same as the added risk
for a multiplicative healthy worker effect

$$\begin{aligned} & [\text{Rate}] \times \text{Healthy Worker Effect} \\ & \times \text{Function (EO dose)} \end{aligned}$$

Basis for Added Cancer Risk Predictions

Mean Response Rate in a Person-Year
= [U.S. 1990 Age-Dependent
Background Leukemia Rate]
 × Function (EO dose)

UCC data based predictions use
Function (EO dose)
estimated from UCC data and Form 2.

NIOSH data based predictions use
Function (EO dose)
estimated from NIOSH data and Form 2.

**Added Cancer Risk Predictions
 (Poisson Regression Analysis: Form 2)
 Environmental Exposure to 1 ppb for 70 years**

Leukemia

Latency: 0 years, No Lag in Exposure

Model with Restricted Parameters	UCC data	NIOSH data
Power	4.2×10^{-10}	1.9×10^{-14}
Polynomial: Linear & Quadratic & Cubic	0.0	0.0
Polynomial: Linear & Quadratic	0.0	0.0
Linear	3.0×10^{-6}	1.0×10^{-6}

Risks Include U.S. 1990 Age-Dependent Competing Risks

**Added Cancer Risk Predictions
 (Poisson Regression Analysis: Form 2)
 Environmental Exposure to 1 ppb for 70 years
Leukemia**

Latency: 10 years, Lag = 5 years

Model with Restricted Parameters	UCC data	NIOSH data
Power	1.8×10^{-6}	7.3×10^{-15}
Polynomial: Linear & Quadratic & Cubic	2.4×10^{-6}	0.0
Polynomial: Linear & Quadratic	4.7×10^{-6}	0.0
Linear	5.0×10^{-6}	1.4×10^{-6}

Risks Include U.S. 1990 Age-Dependent Competing Risks

The

Added Cancer Risk Predictions

using Form 1 and Form 2

are essentially VERY SIMILAR.

**Leukemia is one subset
of Lymphatic and Hematopoietic
responses.**

The UCC and NIOSH added
cancer risk predictions
are very similar when based
on leukemia.

**Lymphocytic Leukemia and
Non-Hodgkin's Lymphoma
is a different subset
(the "lymphoid" subset)
of Lymphatic and Hematopoietic
responses.**

For the "lymphoid" subset, the added cancer risk predictions for an environmental exposure of 1 ppb for 70 years were ALWAYS (for both Forms 1 and 2, the different combinations of latencies and lags, and the different models) less than approximately

$$1 \times 10^{-5}$$

based on the NIOSH data sets
and were ALWAYS

0

based on the UCC data set.

Nonparametric Estimates of the Dose-Response Relationship and Fitted Models

2.0

UCC: Lymphoid Response
Latency = 0, Lag = 0
Form 1

- nonparametric estimate $D = \text{ppm-years}$

The size of the DOT (●) is proportional to the number of person-years. The DOT at 0 ppm-years should be huge.

1.5

Rate Ratio

0.0
0 10 20 30 40 50

ppm-years

$$1 - .0157D$$
$$1 - .240D^{2.856}$$
$$1 - .0434D + .000602D^2$$

0.5

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Nonparametric Estimates of the Dose-Response Relationship and Fitted Models

2.0

**UCC: Lymphoid Response
Latency = 10, Lag = 5
Form 1**

- nonparametric estimate $D = \text{ppm-years}$

The size of the DOT (●) is proportional to the number of person-years. The DOT at 0 ppm-years should be huge.

1.5

Rate Ratio

1.0

0.5

0.0

0

10

20

30

40

50

ppm-years

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For the NIOSH data and the entire set of Lymphatic and Hematopoietic responses, the added cancer risk predictions for an environmental exposure of 1 ppb for 70 years were less than approximately

$$1 \times 10^{-5}$$

based on the linear models but were several orders of magnitude less for polynomial and power models.

UCC

Lymphatic and Hematopoietic Response Data

Workers in ethylene oxide manufacturing who had less than about 250 ppm-years ethylene oxide exposure

had a lower combined lymphatic and hematopoietic response rate

than UCC workers in the same valley who were not involved in ethylene oxide manufacturing.

Animal Bioassay Data:

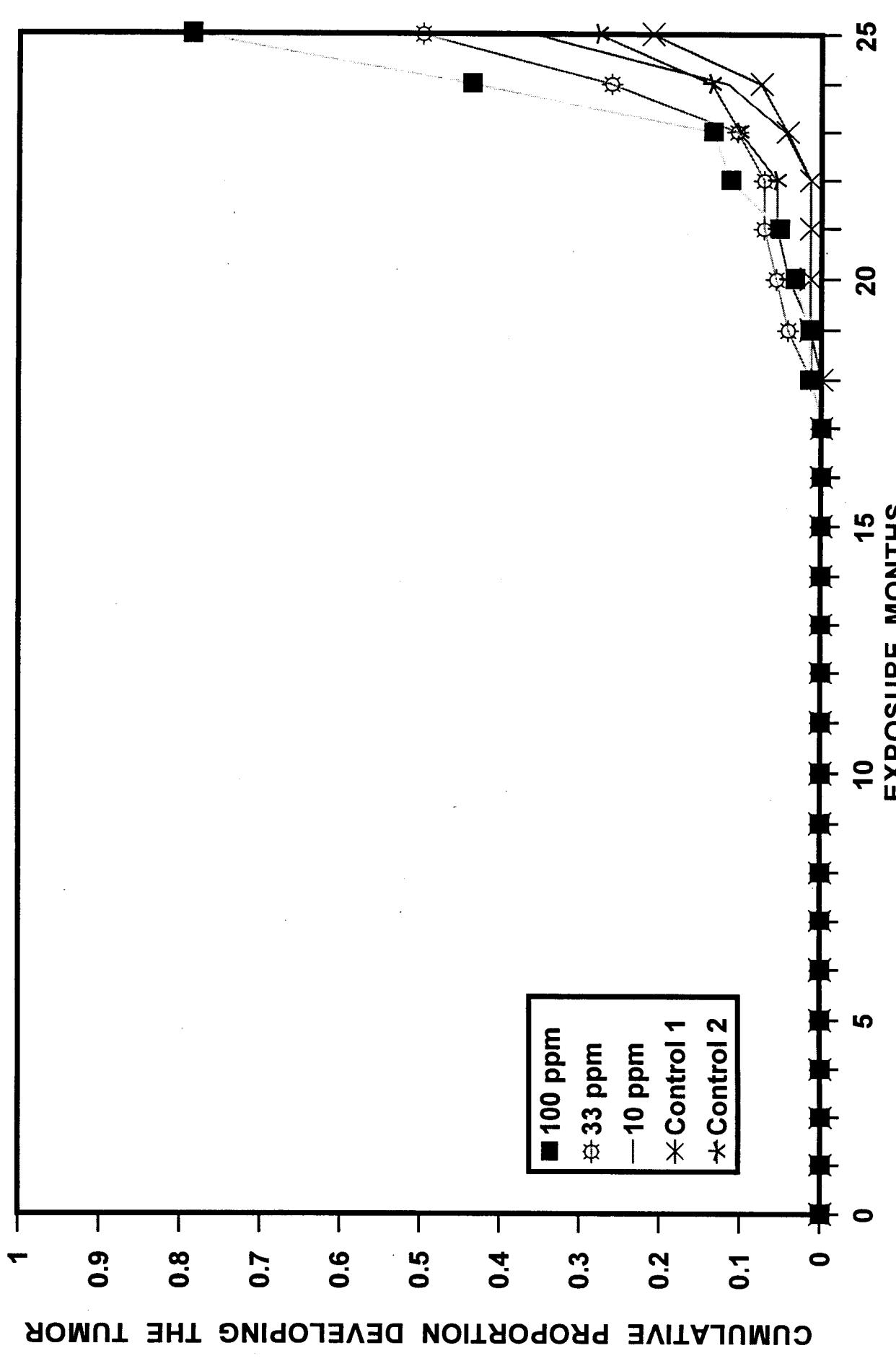
Bushy Run Research Center (BRRC)
Male and Female Rats

NIOSH
Male Rats

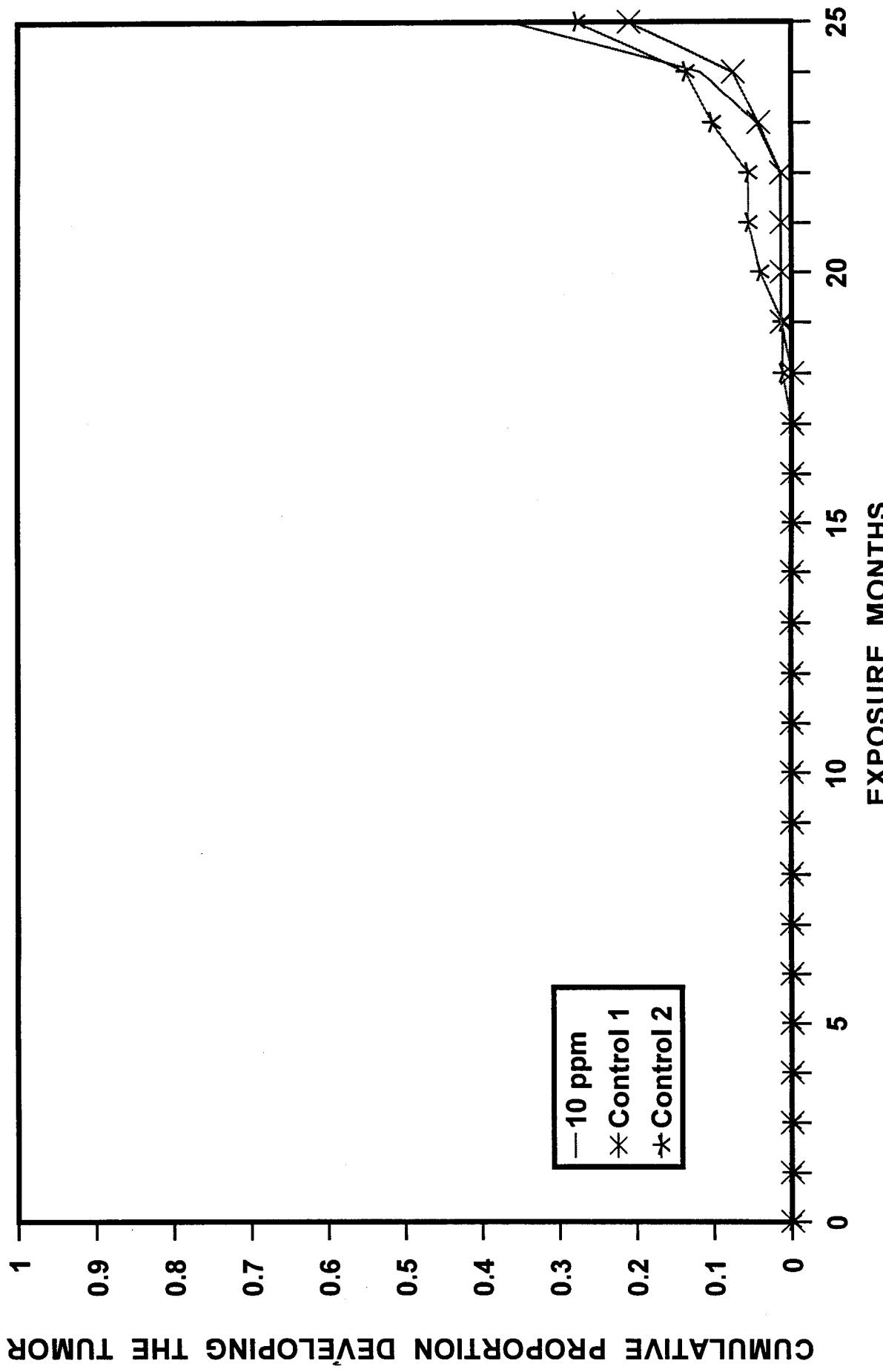
NTP
Male and Female Mice

The Observed Time
of the Carcinogenic Responses
in
Animal Bioassays
is
Very Late

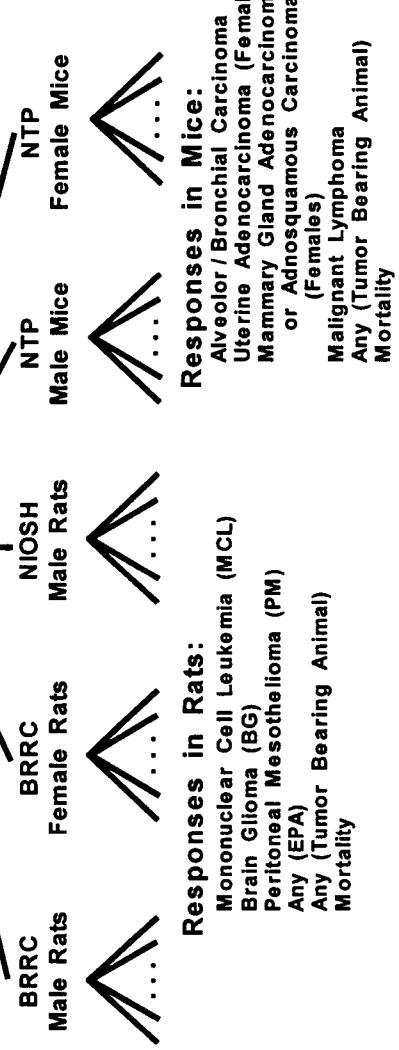
The cumulative proportion of female rats at all exposure levels that developed mononuclear cell leukemia in the Bushy Run Research Center ethylene oxide inhalation study



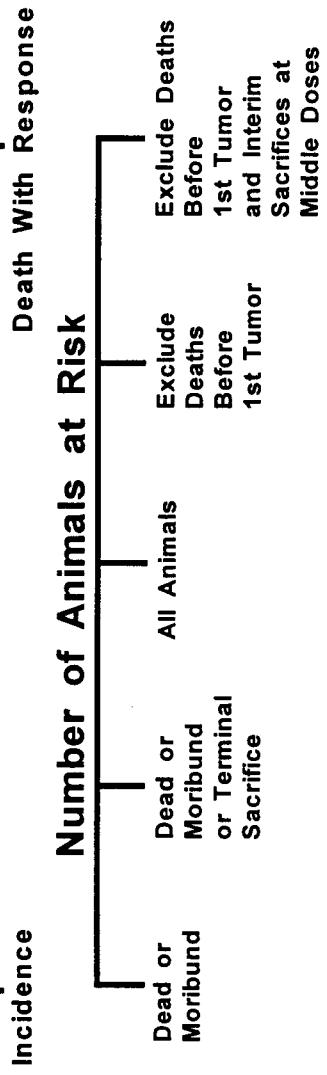
The cumulative proportion of female rats at the control and 10 ppm exposure levels that developed mononuclear cell leukemia in the Bushy Run Research Center ethylene oxide inhalation study



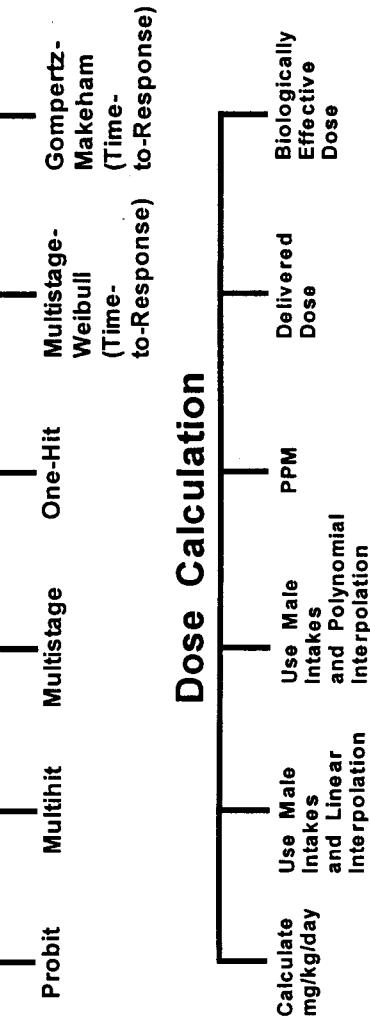
Animal Bioassay Analyses for Ethylene Oxide



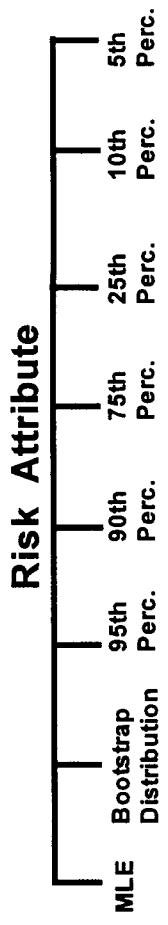
Severity of Response



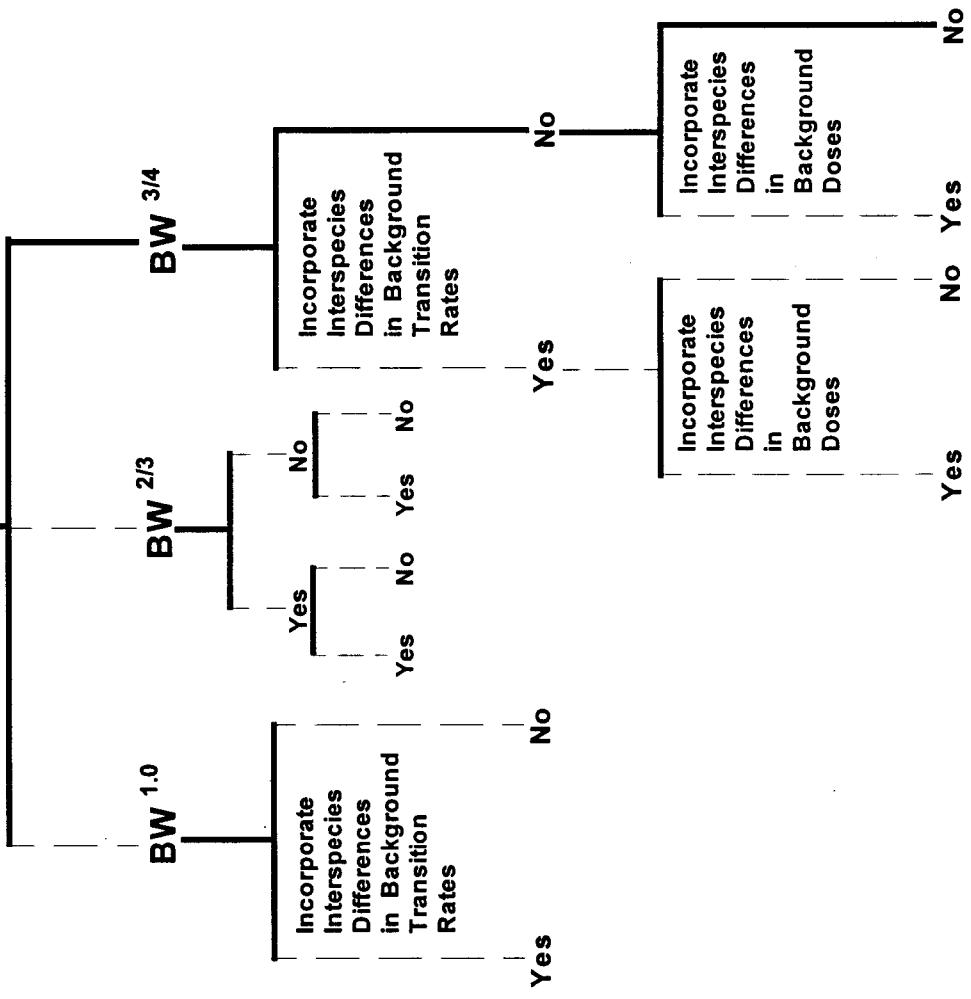
Dose-Response Model



Animal Bioassay Analyses for Ethylene Oxide (Continued)



Interspecies Extrapolation



Interspecies Extrapolation

Based on

Physiologically-Based Pharmacokinetic (PBPK) Modeling

**instead of Default Assumptions
of Species Equivalence
on $BW^{2/3}$ or $BW^{3/4}$ Scales**

**Reduces Estimates of
Human Added Cancer Risks by
4 to 13 Fold**

Interspecies Extrapolation Incorporating

**Interspecies Differences in
Background Transition Rates from Stage to Stage
in a Multistage Carcinogenic Processes**

**instead of Default Assumptions
of Species Equivalence
of Background Transition Rates**

**Reduces Estimates of
Human Added Cancer Risks by
Orders of Magnitude**

Interspecies Extrapolation

**Nonlinearity in Formation
of DNA Adducts at High Doses**

Induction of DNA Repair at Low Doses in Rats

**Humans have Adapted to
Higher Endogenous Levels
than Rats and Mice**

**Not much Interindividual Variability in Humans
in Adduct Levels**

- DNA Adducts
- Hemoglobin Adducts

High-to-Low-Dose Extrapolation Incorporating

**the Required Close Proximity of
Two Genetic Events and the Resultant
Quadratic
Dose-Response Relationship**

**instead of Default Assumptions
of Linearity**

**Reduces Estimates of
Human Added Cancer Risks by
Orders of Magnitude**

On the Road to Incorporating More Science and More of the Available Data into the Dose-Response Assessment of Ethylene Oxide

**Already identified
Large Orders of Magnitude Differences
between Current Regulatory Risk Assessment
and the New Perspectives
obtained on that Road**

Ethylene Oxide Epidemiology

Implications for

Cancer Risk Assessment

Society for Risk Analysis

December 10, 1997

M. Jane Teta, Dr.PH

Implications for Risk Assessment

- ❖ Cancer Data for Large Numbers of EO Workers
- ❖ Two Epi Studies Have Exposure Estimates Usable for risk estimation
- ❖ Epi & Animal Data Suggest Focus on Lymphohematopoietic Cancers
- ❖ Models and Estimates of Added Risk Should Account for Latency, Age-Dependent Exposures, Competing Risks, Model Fit, Comparison Groups, Healthy Worker Effect

UCC/NIOSH Study Characteristics

NIOSH

- ❖ n=1,896 ❖ n=18,254
- ❖ 23 % deceased ❖ 6.4% deceased
- ❖ ave. duration ,5.4 yr. ❖ ave. duration 4.9 yr.
- ❖ ave. follow up 27.2 yr. ❖ ave. follow up 16.1 yr.
- ❖ ave. 1st exp. 1961 ❖ ave. 1st expo. 1970
- ❖ leukemia 5 observed ❖ leukemia 11 observed
- ❖ lymphoid 3 observed ❖ lymphoid 19 observed
- ❖ exposure:indirect est. by decade & intensity ❖ exposure:indirect est. by modeling predictors

Hazard Summary

- ❖ Human Evidence Does Not Indicate EO Causes Increased Risk of Cancers Overall, Brain, Stomach or Pancreatic Cancer
- ❖ Findings for certain Lymphohematopoietic Tissue Cancers Less Definitive
- ❖ Females Do Not Appear to Be More Sensitive

Stayner Uncertainties

- ❖ Impact of Few Highly Exposed Cases
(Max = 1356 ppm Yr)
- ❖ SMR Life-Table Approach Non Positive
- ❖ Inverse Relationship for Females
- ❖ Choice of Model

Stayner Results

- ❖ Stat. Sig. Relation Between Cum. Exposure and “Lymphoid” Cancers
- ❖ Weaker Positive Associations with Non Hodgkin’s lymphoma and leukemia (Not stat. sig.)
- ❖ Inverse Relation with Stomach, Kidney, Pancreas and Brain
- ❖ No Associations with Other Exposure Metrics

Stayner Exposure-Response

Analysis of Steenland Data

- ❖ Cancer Mortality Data and Individual Exposure Estimates for Workers from 13 Medical Products/Spice Plants
- ❖ Exposure Metrics: Cumulative, Duration, Average, Maximum
- ❖ Cox Proportional Hazards Model

Epidemiology Exposure Information

- ❖ Individual Ave. Exposure Estimates

- NIOSH Study (*Steenland/Stayner*) of 18,254 Sterilant Workers (*Historical Reconstruction*)
- Hagmar Study of 2,170 Sterilant Workers (*Air Concentrations & Hemoglobin Adducts*)
- Teta Study of 1,896 Chemical Workers (*Time Period Ranges*)

- ❖ Others Qualitative, Means, 1970s+ Levels

- ❖ Peak Exposures Occurred, but Not Well Quantified

Current Sources of Tumor Data

Epidemiology Studies

- ❖ 12 Cohorts of Over 33,000 Workers, More Than 800 Cancers, in 5 Countries Producing or Using EO
- ❖ Average Follow Up, 7-28 Yr (Max = 53 Yr)
- ❖ Average Duration of “Exposure”, Up to 10 Yr
- ❖ First Exposures < 1940 for Several Cohorts

Sources of Tumor Data

Chronic Bioassays

- ❖ Fischer 344 Rats – Snellings et al., 1984
 - Lynch et al., 1984
 - *Increased Incidence of Mononuclear Cell Leukemias, Brain Tumors, Peritoneal Mesothelioma*

- ❖ B6C3F1 Mice – NTP, 1988
 - *Lung, Uterine, Mammary Tumors, Lymphoma*

EO Meta-Analysis*

- ❖ Qualitative/Quantitative Assessment
- ❖ Magnitude and Consistency of Risk Estimates
 - ❖ Tests of Heterogeneity
 - ❖ Trends by Intensity/Frequency of Exposure, Duration, Latency
- ❖ Consideration of Confounding Exposures
- ❖ Updated with two new studies

*Shore Et Al., BJM 1993;50:971-997

EO Epi Studies

Author	Country	Workers	Cancers	Ave.	Dur.	Ave.	Obs
Hogstedt	Sweden	240	7	4-9		?	
Hogstedt	Sweden	175	20	3-30		?	
Hogstedt	Sweden	355	13	9-13		?	
<i>Hagmar</i>	Sweden	2,170	40	?		11.6	
Thiess	Germany	602	12	11		14	
Kieselbach	Germany	2,658	68	9.6		15.5	
Morgan/Divine	U.S.	767	19	>20		?	
Greenberg/Teta	U.S.	1,896	110	5.4		27.2	
Steenland	U.S.	18,254	343	4.9		16.1	
Bisanti	Italy	1,971	43	~7		~9	
Gardner	UK	2,876	85	?		?	
Olsen	U.S.	1,361	75	5.7		24.5	

Risk Ratios According to Sex

	Steenland et al.		Gardner et al.		Hogstedt	
	Men n = 8,214	Women n = 10,040	Manuf. n = 1,471	Hosp. n = 1,405	Men n = 539	Women n = 170
All Cancer	0.99	0.82	1.14	1.07	1.58	2.12
Leukemia	1.16	0.77	2.26	0	6.11	9.09
Brain Ca.	0.86	0.17				
LH*-Leuk	1.81	0.39			1.92	0
Non Hodgkins			1.04	0.57		
Breast	0.85 (42obs., 50exp.)					

* Lymphohematopoietic
- Not Available

EO Meta-Analysis Findings

Endpoint	O/E	Meta SMR	95% CI	Duration	Intensity Latenc
All Causes	2840/3628	0.78	(0.73, 0.84)		
All Cancer	876/928	0.94	(0.85, 1.05)		
Pancreas	37/39	0.95	(0.69, 1.31)	No	No
Brain	25/26	0.96	(0.49, 1.91)*	No	Yes
Stomach	59/48	1.23	(0.71, 2.13)*	No	No
Leukemia w/o Hogstedt	35/32	1.08	(0.77, 1.50)	No	No
	30/31	0.96	(0.61, 1.93)*		
Non Hodgkins	33/25	1.34	(0.96, 1.89)	No	No

* Adjusted for Heterogeneity

Based on 4 Studies with Latency Data for Brain Cancer

Prior EPA EO Risk Assessment 1985

- ❖ Mononuclear cell leukemias and brain gliomas in the female rat (Snellings et al. 1981)
- ❖ Linearized multistage model
- ❖ 95% upper-limit unit risk (8 X OSHA)
- ❖ Excess lifetime cancer risk for humans (1 ppm) = **19%**
- ❖ Estimates based on Hogstedt 1979 cluster report do not contradict estimate based on rat inhalation

